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09/537,654	03/29/2000	Pramod B. Mahajan	1107	7300

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EXAMINER
KUBELIK, ANNE R

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 07/01/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/537,654	Applicant(s) MAHAJAN ET AL.	
	Examiner Anne Kubelik	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The cancellation of claims 1 and 11, the amendment of claims 2, 7 and 9-10, and the addition of new claims 12-15 requested in Paper No. 10, filed 15 April, 2002, have been entered, as have the amendments to the specification, title and abstract. Claims 2-10 and 12-15 are pending.

2. In the response filed 15 April, 2002, Applicant again argues the restriction. Applicant again argues that the nucleic acids of SEQ ID NOs:1, 3 and 5 have over 99% sequence identity (as shown in Appendix A) and thus one search would encompass them all (response pg 8-9).

This is not found persuasive because a thorough examination of the claims in the instant application requires individual searches on each of the sequences against all the PTO databases.

The restriction requirement remains FINAL.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The title of the invention is not descriptive of the instant invention. The instant invention is drawn to a RAD51 gene, not to the protein. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

Response to Amendment

5. The rejection of claims 1-3 under 35 U.S.C. 102(b) as being anticipated by each of Buchert et al and Rounsley et al is WITHDRAWN in light of cancellation of claim 1 and because claim 15 is drawn to a nucleic acid comprising 50 contiguous nucleotides of SEQ ID

NO:1, and claim 12 is at its broadest drawn to a nucleic acid having 80% identity to SEQ ID NO:1 that encodes a protein with RAD51C activity.

6. The rejections of claims 1-4, 6 and 8-9 under 35 U.S.C. 103(a) as being unpatentable over Reiss et al in view of Rounsley et al and claims 5, 7 and 10 under 35 U.S.C. 103(a) as being unpatentable over Reiss et al in view of Rounsley et al and further in view of Gordon-Kamm et al are WITHDRAWN in light of the cancellation of claim 1, because claim 15 is drawn to a nucleic acid comprising 50 contiguous nucleotides of SEQ ID NO:1, and because claim 12 is at its broadest drawn to a nucleic acid having 80% identity to SEQ ID NO:1 that encodes a protein with RAD51C activity.

Claim Objections

7. Claims 9 and 12-15 are objected to because of the following informalities:

There is an improper article before "polynucleotide" in claim 9, line 4, claim 12, line 5, claim 13, line 3, claim 14, line 3, and claim 15, line 2.

There is an improper article before "polypeptide" in claim 12, line 6.

Claim Rejections - 35 USC § 101

8. Claim 14 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility. The rejection is repeated for the reasons of record as set forth in the last Office action mailed 8 November, 2001, as applied to claims 1-10.

Applicant's arguments filed 15 April, 2002, have been fully considered but they are not persuasive. Applicant urges that the specification teaches a specific use for the nucleic acids claimed in a method to modulate the level of RAD51C in a plant, and that subsequences of the nucleic acid could be used in that method. Applicant urges that claims have been amended to recite nucleic acids that comprise at least 50 contiguous nucleotides of SEQ ID NO:1, thus excluding the nucleic acids recited in the rejection (nucleic acids encoding a mannanase, a DNA repair protein, or RAD57) (response pg 9-12).

This is not found persuasive because polynucleotides comprising at least 100 contiguous nucleotides that selectively hybridize to SEQ ID NO:1 include a human nucleic acid with homology to DNA repair proteins (NCI-CGAP, 1998, GenBank Accession No. AI184177). The instant specification fails to teach the specific use of such nucleic acids.

9. Claim 8 remains rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility. The rejection is repeated for the reasons of record as set forth in the last Office action mailed 8 November, 2001.

Applicant's arguments filed 15 April, 2002, have been fully considered but they are not persuasive. Applicant urges that because claim 8 depends from claim 4, which claims a transgenic plant comprising the recombinant expression cassette of claim 2, the requirement for comprising the expression cassette carries into claim 8 (response pg 12).

This is not found persuasive because half the seeds produced from the plant of claim 4 will have the recombinant expression cassette and half will not. "Transgenic seeds" could contain some other transgene, such as a transposon. A requirement that the parent plant have the cassette does not mean that the seeds will have it. The instant specification fails to teach the

specific use of a transgenic seed that does not comprise the expression cassette of claim 2. It is suggested that the claim be amended to require that the seeds have the recombinant expression cassette.

Claim Rejections - 35 USC § 112

10. Claim 14 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The rejection is repeated for the reasons of record as set forth in the last Office action mailed 8 November, 2001, as applied to claims 1-10.

Applicant's arguments filed 15 April, 2002, have been fully considered but they are not persuasive. Applicant urges that this rejection should be withdrawn for the reason stated above.

This is not found persuasive for the reason stated above.

11. Claims 2-10 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids of SEQ ID NO:1 or that encode SEQ ID NO:2, does not reasonably provide enablement for nucleic acids that have 80% identity to SEQ ID NO:1, that are amplified from primers that hybridize under unspecified stringency to "loci within" SEQ ID NO:1, or that comprise 100 nucleotides that hybridize to SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the last Office action mailed 8 November, 2001, as applied to claims 1-10.

Applicant's arguments filed 15 April, 2002, have been fully considered but they are not persuasive. Applicant urges that the specification provides guidance for modification of the nucleic acids and proteins of the instant invention, and cites many pages of the specification. Applicant also urges that the specification teaches conserved sequences in the RAD51 family, particularly in example 4. Applicant also urges that at the time of filing it was within the ability of one of skill in the art to determine which amino acids could be altered because methods for assaying functions and phenotypes of RAD51 homologies were well-known. Applicant urges that references in the IDS filed 23 June, 2000, cite assay methods that include yeast-two-hybrid screens, DNA strand exchange, complementation, homologous recombination, and gamma irradiation. Applicant also urges that RecA could be used to model the structure of RAD-51 like sequences. Applicant urges that Bowie teaches that proteins are highly tolerant of amino acid substitutions and that Reiss et al teach that RecA did increase the fidelity of recombination and they suggest that there may have been no increase in gene targeting because of unavailability of the ssDNA substrate in the transformation method used. Applicant urges that the nucleic acids of the instant invention do not encompass non-RAD51-like nucleic acids (response pg 13-17).

This is not found persuasive. The pages of the specification pointed to as providing guidance for making variants, for sequence comparison and analysis, for amplification of nucleic acids, for hybridization and for subsequences only provide general guidance and do not teach the specific probes, conditions, etc, needed to isolate the claimed nucleic acids. Similarly, the references cited in the IDS do not teach the specific methods relevant to the instant nucleic acid.

See *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling

disclosure", and that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Undue experimentation would have been required by one skilled in the art to develop and evaluate RAD51C-encoding nucleic acids encoding proteins with 80% identity to SEQ ID NO:2. Making all possible single amino acid substitutions in an 294 amino acid long protein like that encoded by SEQ ID NO:1 would require making and analyzing 19^{294} nucleic acids; these proteins would have 99.7% identity to SEQ ID NO:1. Because nucleic acids encoding proteins with 80% identity to SEQ ID NO:2 would encode proteins with 59 amino acid substitutions, many more than 19^{294} nucleic acids would need to be made and analyzed. The *Arabidopsis* RAD51C protein has only 185 amino acids in common with that of SEQ ID NO:2. Even using this as guidance means there are still 19^{109} nucleic acids that would need to be made and analyzed.

As the specification does not describe the transformation of any plant with a gene encoding the nucleic acid of SEQ ID NO:1, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with modulated RAD51C, if such plants are even obtainable.

Bowie et al, Lazar et al, and Hill et al, cited in the prior Office action, teach that even for proteins that have been highly studied or for which many homologues exist, making protein substitutions is unpredictable. The substitution of glutamic acid for aspartic acid is the sort of substitution suggested on pg 8 of the specification. However, Lazar et al showed that this

substitution reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract).

Reiss et al propose a variety of explanations and mechanisms for the functioning of RecA in plants, and states that ssDNA should be generated during repair and replication. None of these explanations detracts from the fact that the enzyme did not act as expected.

Lastly, the instant specification fails to teach how nucleic acids including a human nucleic acid that does not encode RAD51, as discussed in the 35 USC 101 rejection above, could be used to modulate the level of maize RAD51 in a plant.

12. Claims 2-10 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the last Office action mailed 8 November, 2001, as applied to claims 1-10.

Applicant's arguments filed 15 April, 2002, have been fully considered but they are not persuasive. Applicant urges that claim 12 recites the function of the protein in the preamble. With respect to the plants, Applicant asserts that the phenotype of the transgenic plants will depend on the orientations of the recombinant expression cassettes and the nature of the promoters used. Applicant urges that Dosanjh teach a different member of the RAD51 gene family. Applicant urges that the instant specification provides guidance for methods of making the nucleic acids of the instant invention (response pg 17-20).

This is not found persuasive because the instant specification does not teach RAD51C encoding nucleic acids with 80% identity to SEQ ID NO:1 or that can be amplified from a maize library, or an isolated nucleic acid that comprises 50 contiguous nucleotides of SEQ ID NO:1.

Claim 15 recites no description of the function of the protein encoded by the nucleic acid and the plant claims recite no phenotype.

See *In re Shokal,* 113 USPQ 283, (CCPA 1957) at pg 285

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary. ...
> We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.

13. Claims 2-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Neither the instant specification nor the originally filed claims appear to provide support for the phrase "over the entire length of the reference sequence" in claim 12, part (a). Thus, such phrase constitutes NEW MATTER. In response to this rejection, Applicant is required to point to support for the phrase or to cancel the new matter.

14. Claims 2-10 and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that

Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is repeated for the reasons of record as set forth in the last Office action mailed 8 November, 2001, as applied to claims 1-10.

Applicant's arguments filed 15 April, 2002, have been fully considered but they are not persuasive.

Claims 13 and 14 are indefinite in their recitation of "selectively hybridizes" and "stringent hybridization conditions". What would be considered selective or nonselective hybridization and what level of stringency is considered selective or stringent is unclear.

In claim 14, the time for which the wash is done is unclear.

Applicant urges that hybridization is a common technique and that the specification defines "selective hybridization" and "selectively hybridizes" on pg 14, line 30, to pg 15, line 3, and defines wash conditions on pg 16-17. Applicant urges that one of skill in the art would understand the bounds of the claim when read in light of the specification (response pg 20-22).

This is not found persuasive because pg 14, line 30, to pg 15, line 3, provide examples of conditions that would be considered "selective" and "stringent" and pg 16-17 define a variety of exemplary wash conditions but none of these pages define what Applicant actually intended the terms to mean. In the art, these terms have widely divergent meanings, with different researchers having different definitions of the terms. Thus, one of skill in the art would not understand the bounds of the claim when read in light of the specification. It is suggested that Applicant amend the claims to recite specific hybridization and wash conditions (*i.e.*, salt concentration, temperature and times), choosing the intended conditions from the multitude listed in the specification.

In claim 12, "comprising" in line 2 should be replaced with --, wherein the polynucleotide comprises--. Currently, the phrase starting with "comprising" modifies "activity".

Claim 13 is indefinite in its recitation of "amplified ... to loci within". It is not clear what those loci are or their size. Additionally, the size of the amplified polynucleotide is not clear.

Claim Rejections - 35 USC § 102

15. Claim 14 is rejected under 35 U.S.C. 102(a) as being anticipated by NCI-CGAP (1998, GenBank Accession No. AI184177). The rejection is repeated for the reasons of record as set forth in the last Office action mailed 8 November, 2001, as applied to claims 1-3.

Applicant's arguments filed 15 April, 2002, have been fully considered but they are not persuasive. Applicant urges that NCI-CGAP does not teach a nucleic acid of 100 nucleotides that would hybridize under stringent conditions to SEQ ID NO:1

This is not found persuasive because the nucleic acid taught by NCI-CGAP would "selectively hybridize" to SEQ ID NO:1 under at least one of the multitude of hybridization and wash conditions the specification defines as "selective".

16. Claims 2-10, 12-13 and 15 are free of the prior art given the failure of the prior art to teach or suggest an isolated RAD51C encoding nucleic acid with 80% identity to SEQ ID NO:1, that encodes SEQ ID NO:2, or that can be amplified from a maize library, or an isolated nucleic acid that comprises 50 contiguous nucleotides of SEQ ID NO:1.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kimberly Davis, at (703) 305-3015.

Anne R. Kubelik, Ph.D.
June 25, 2002

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638